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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/765,324	12/24/1996	EUGEN KOREN	OMRF143-CIP2	5919

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EXAMINER
DUFFY, PATRICIA ANN

ART UNIT	PAPER NUMBER
1645	34

DATE MAILED: 12/05/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/465,324	Koren. et al
Examiner	**Group Art Unit**
DUFFY	1645

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on CPA of 9-4-01 + Amendment of 9-14-01.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Dispositi n of Claims

☒ Claim(s) 48-51 is/are pending in the application.

Of the above claim(s)____ is/are withdrawn from consideration.

☐ Claim(s)____ is/are allowed.

☒ Claim(s) 48-51 is/are rejected.

☐ Claim(s)____ is/are objected to.

☐ Claim(s)____ are subject to restriction or election requirement.

Applicati n Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on____ is/are objected to by the Examiner.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s).____

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other____

Office Action Summary

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 9-4-01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/765,324 is acceptable and a CPA has been established. An action on the CPA follows.

2. The amendment filed 9-4-01 has been entered into the record. Claims 48-51 are pending and under examination.

Rejections Withdrawn

3. The rejection of claims 48, 50 and 51 under 35 U.S.C. 102(b) as being clearly anticipated by Lee et al (Biochimia et a Biophysica Acta, 666:133-146, 1981) is withdrawn in view of the amendments to the claims. It is noted that the amendments to the claim recite new matter for the reasons set forth below and in the event that the new matter is removed the rejection will be reinstated.

4. The rejection of claims 48, 49, 50 and 51 under 35 U.S.C. 103(a) as being unpatentable over Lee et al (Biochimia et a Biophysica Acta, 666:133-146, 1981) in view of Gooding, J.W., (in Monoclonal Antibodies, Academic Press Inc., Orlando, Florida, 1983, p 56-97) is withdrawn in view of the amendments to the claims. It is noted that the amendments to the claim recite new matter for the reasons set forth below and in the event that the new matter is removed the rejection will be reinstated.

5. The rejection of claims 48, 50 and 51 under 35 U.S.C. 103(a) as being unpatentable over Lee et al (Biochimia et a Biophysica Acta, 666:133-146, 1981) in view of Zhou et al (Acta Acad Med Hubei, 11(4):298-302, 1990) and Mills et al (in Laboratory Techniques in biochemistry and molecular biology, a guidebook to lipoprotein technique, Elsevier, 1984, pages 384-448) is withdrawn in view of the amendments to the claims. It is noted that the amendments to the claim recite new matter for the reasons set forth below and in the event that the new matter is removed the rejection will be reinstated.

New and Maintained Rejections

6. The rejection of claims 48-51 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons made of record and new reasons set forth below.

Applicants' arguments have been again carefully considered but are not persuasive. The relied upon passages are at pages 27 and 47 of the specification. At page 27 the specification recites:

> "To obtain an anti-LDL MAb whose binding to LDL particles is not dependent on variations in LDL composition and/or conformation, mice were immunized with soluble ApoB-100 which had been delipidized, reduced, carboxymethylated and, purified by electrophoration in polyacrylamide gels containing 8 M urea (Lee, D. M. et al, Biochim. Biophys. Acta, 666:133-146(1981)). Immunization with such delipidized, soluble, reduced, carbozymethylated, and electrophoretically purified Apo B-100 has not been previously reported."

At page 47 the specification recites:

> "The MAb to Apo B, HB3cB3, was produce by immunizing mice with Apo B-100 molecules which had been delipidized, reduced, carboxymethylated and purified by electrophoresis on a polyacrylamide gel containing 8M urea. Delipidized ApoB-100 readily precipitated due to self-aggregation in aqueous media. In addition to self-aggregation, ApoB-100 is also susceptible to fragmentation during the solubilization procedure (Soccorro, L. and Camejo, G. J. Lipid Res., 20:631-645, (1979); Olofsson, S. O. et al., Biochemistry, 19:1059-1064, (1980)). Therefore, in order to separate self-aggregated and degraded material from the preserved protein, the delipidized, reduced, and carboxymethylated ApoB-100 was electrophoresed on a polyacrylamide gel containing 8 M urea. Coomassie blue staining of the urea-polyacrylamide gel was cut out immediately after the completion of electrophoresis and subcutaneously injected (while still in the gel) into mice without further manipulation of addition or adjutants."

It is noted that the written description in these passages directed to the apolipoprotien immunogen do not convey conception of: (a) the subgenus of solubilization with a reducing or denaturing agent as is instantly claimed; (b) removeal of all self-aggregated and degraded material (i.e. free from self-aggregated and degraded material) by any means; (c) soluble lipoprotein (LDL, HDL or VLDL) as an immunizing material; (d) immunization with a apolipoprotein that is delipidated, reduced, carboxymethylated and solubilized with a reducing or denaturing agent that is free from aggregates and degradation products and (e) polyclonal antibodies.

The relied upon passage still does not support the claimed immunogen or the new subgenus of solubilization. As to point (a) the cited passages of the specification do not convey the subgenus means of solubilization as is now claimed. The only order provided by this passage is that the purification by electrophoration in polyacrylamide gels occurred subsequent to solubilization, delipidization, reduction and carboxymethylation. Moreover, it is the soluble Apo B-100 that is reduced. This passage conveys reduction as a separate process from solubilization. The passage does not specify how the ApoB-100 was solubilized and thus the amendment to provide solubilization with a reducing or denaturing agent provides a new subgenus of agents that is not supported by the origional written description and is therefore considered new matter. The recitation of the genus of solubilization does not provide written descriptive support for more narrowly claiming solubilization by a reducing or denaturing agent. This new subgenus of solubilizing agents/methods has no conception in the specification as originally filed. Moreover, to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention and that the invention, in that context, is whatever is now claimed.. See MPEP 2163.02. Also, the failure to meet the written description requirement under 35 U.S.C. 112, first paragraph arises when the claims are changed after the filing date to change the scope of the disclosure, which does encompass setting forth subgeneric claims (see MPEP 2163.05). As to point (b) applicants argue that the free of all self aggregated and degraded material is presumably the result obtained using polyacrylamide gel

electrophoresis on page 47. This is not persuasive. Electrophoresis may or may not remove all self aggregated and degraded material. Applicants are presumably relying upon an putative inherent property of a particular process, yet that process limitation is not in the claim. Moreover, presumption is not a showing of inherency. The inserted property, must necessarily flow from the process of the specification. Moreover, with respect to applicants opinion, the methods of purification of page 42-43 rely upon antibody binding and as such do not, and can not, discriminate between the degraded and aggregated apolipoproteins as opposed to that which is not degraded and aggregated. The generic teachings of immunoaffinity purification will not distinguish these characteristics. The antibodies of the art do not distinguish based upon size and degradation and bind all forms of the apolipoprotein. Applicants should thus explain the scientific basis that provides for their basis for asserting that a generic immunoaffinity method as provided in the relied upon passages necessarily provide for the recited limitations. Therefore. Applicants' opinion is unsubstantiated and contrary to general scientific teachings in regard to immunoaffinity purification. As to point (c), neither the passage at page 27, nor page 47 provides for conception of a lipoprotein so processed as an immunogen, nor how to utilize gels to remover all self aggregated and degraded from the lipoproteins (LDL, HDL or VLDL). The treatment regimen would destroy the lipoprotein as defined by the art. No purification of a lipoprotein free of self aggregated and degraded material can be made. The specification provides no written description of how to purify lipoproteins so treated. The teachings of the specification are limited to purification of the apolipoprotein components of the lipoprotein. As such, the amendment of the claims to recite lipoproteins are processed and purified is deemed new matter. As to point (d), the immunogen used in this specification was not solubilized and reduced. At page 47, the specification teaches that the animal was immunized as "The most prominently stained band in the urea- containing polyacrylamide gel was cut out immediately after completion of electrophoresis and subcutaneously injected (while still in gel) into mice without further manipulation of addition or adjutants". As such, the immunogen of the specification was not administered in a solubilized and reduced form as now claimed. Solubilized by

means of convention for proteins is in dissolved in fluid. Secondly, there is no indication in the written description that the polyacrylamide/urea gel used to purify the apolipoprotein and gel used to immunize the animal contained any reducing agent. As such, there is no written description basis for claiming that the immunogen was "reduced" or "solubilized" at the time of immunization as is instantly claimed. Moreover, the passage at pages at page 27 and 47 indicates that reduction was performed before processing to remove self-aggregated and degraded material and that the starting material was a "solubilized" apolipoprotein. Moreover, solubilization as set forth by references in the specification and by art accepted convention, does not include polyacrylamide/urea gel electrophoresis as a means for solubilization. By no means can injection in a polyacrylamide/urea gel be considered "solubilized" as set forth in the claims. Lee et al of record sets conventional solubility definition in this art "A test of true solubility was made by centrifuging the solution at 12,000 xg for 30 min. in an Eppendorf centrifuge 3200. No precipitate of gel formation was observed. " (see page 136, second full paragraph). Moreover, the specification at page 47 defines the polyacrylamide/urea gel as a purification step and not a solubilization step and further does not state that the polyacrylamide/urea gel was in fact a reducing gel. As such, the immunogen set forth in the specification is neither reduced nor solubilized as is now claimed. As such, Applicants are mixing and matching concepts and method steps to arrive at an immunogen that has no written description support in the specification as originally filed. As to point (e), the passages are devoid of any mention of polyclonal antibodies and as such is considered new matter.

Applicants' arguments are insufficient to obviate the rejection.

7. The rejection of claims 48-51 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making a monoclonal antibody which specifically binds a stable, conformationally independent epitope which is uninfluenced by the lipid content of an apolipoprotein and lipoprotein, comprising: (a) immunizing an animal with a delipidized, soluble, reduced, carboxymethylated and electrophoretically purified apolipoprotein; (b) producing hybridomas from a spleen isolated from the immunized animal; and © screening for

a monoclonal antibody which specifically binds a stable, conformationally independent epitope which is uninfluenced by the lipid content of an apolipoprotein and lipoprotein, it does not reasonably provide enablement for generically antibodies (i.e. polyclonal and monoclonal) or immunizing with an lipoprotein which has been dilapidated, reduced, solubilized and purified. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims is maintained for reasons made of record.

Applicants' arguments have again been carefully considered but are not persuasive. Applicants appears to argue the examiner has not set forth and has not provided any art or basis for the rejection and that the specification clearly enables all in light of the general applicability of the methodology and should not be so limited. This argument is not understood the basis has been clearly set forth in the rejection of record and art provided. Applicants assert that it is well establishes that when an animal is immunized that the result is polyclonal antibodies. Applicants assertion is contrary to the widely held tenets of immunology. Any Immunology textbook demonstrates that immunizing antigens can provide a variety of immune responses, such as cytotoxic T cell (cell-mediated responses), T suppressor cells (clonal anergy or clonal suppression) or delayed type hypersensitivity responses (Th1-mediated). None of these immune responses to antigens require antibody production, all require immunization with an antigen. Therefore immunization does not necessarily result in antibody production as Applicants allege. It is noted that applicants claims are drawn to a preamble that recites "A method of making an antibodies to an epitope of an apolipoprotein or lipoprotein which reacts with apolipoprotein or lipoprotein independently of lipid content and conformation of the apolipoprotein or lipoprotein." It is noted that the claims are not drawn to a method of making an antibody as argued by Applicants. Applicants argue that since the immunization produces a monoclonal antibody that has the particular recited binding properties, then they are logically entitled to polyclonal antibodies having the same binding property because clearly at least one of the antibodies in the polyclonal preparation have the required binding properties. Applicants argue that immunization of an animal to produce

only the same type of antibodies, reactive with a single epitope has never been achieved and therefore they are enabled for polyclonal antibodies. This is not persuasive because Applicants provide the very reason that the are not enabled, the immunization procedure does not result in a polyclonal antibody that produces only the same type of antibodies that bind the epitope as claimed. The examiner has provided evidence of unpredictability of production of polyclonal antibodies, applicants admit that there are other antibodies present than that claimed.

The rejection is maintained.

8. The rejection of claims 48-51 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps is maintained for previously made of record.

The method is missing critical steps the preamble recites a method of making antibodies and no such antibodies are screened for or isolated. Moreover, as discussed directly above, immunization does not necessarily provide for antibody production. Applicants' arguments that immunization necessarily provides for antibody production is scientifically incorrect and not persuasive. Applicants are not claiming a method of immunization but a method of making antibodies and no antibodies are in fact produced or isolated. The claims remain incomplete for reasons made of record.

Specification

9. The amendment filed to amend the abstract is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the passage on page 27 of the specification does not support generic antibodies for the same reasons as the claims do not. As such, the amendment of the specification to broadens the scope of the disclosure introduces new matter.

Applicant is required to cancel the new matter in the reply to this Office action.

Status of Claims

10. No claims are allowed.

11. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Sunday-Thursday from 9:30 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308-3909.

Patricia A. Duffy, Ph.D.
December 2, 2001

Patricia A. Duffy

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600